Comparison of the Efficacy of Standard Epithelium-off Corneal Collagen Cross-linking and Iontophoresis-assisted Transepithelial Corneal-collagen Cross-linking in the Treatment of Keratoconus: A Systematic Review

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ABSTRACT

Purpose: Keratoconus is an ectatic corneal condition characterised by progressive thinning and steepening of the cornea. Corneal collagen cross-linking (CXL) is a treatment aimed at halting keratoconus progression by increasing corneal rigidity. Of the various techniques, epithelium-off (S-CXL) is the current gold standard. Epithelium-on methods are favourable as the intact epithelium reduces pain and risk of infection, however riboflavin permeability is reduced. Iontophoresis-assisted transepithelial CXL (I-CXL) was developed to overcome this. This systematic review compares the efficacy of I-CXL against S-CXL at halting keratoconus progression to determine if I-CXL could become the new gold standard.

Methods: A search was performed across Medline, Embase and CINAHL, alongside citation searching, and hand searching of the Australian Orthoptic Journal. Studies comparing I-CXL with S-CXL were included. Critical appraisal and data extraction were performed to conduct a narrative synthesis.

Results: Seven studies of 378 were deemed eligible for inclusion. All studies found I-CXL to be a safe technique for stabilising keratoconus progression, producing results that were either comparable or inferior to S-CXL results. However, no definitive conclusion can be drawn regarding the efficacy of I-CXL against S-CXL due to the limited number of studies included, their small sample sizes and the influence of bias.

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INTRODUCTION

Keratoconus is a form of corneal ectasia[1] that causes progressive thinning and steepening of the cornea,[2] which impairs vision by inducing myopia and irregular astigmatism.[3,4] Keratoconus prevalence varies between geographical areas,[3,5] however a systematic review from 2020 found worldwide prevalence to be 1.38 per 1,000 population.[6] Patients are usually asymptomatic at onset[3] yet will eventually experience blurry or distorted vision, and typically require frequent adjustment to optical correction due to refractive instability.[4,7] Keratoconus is believed to be a multifactorial condition, resulting from an intricate combination of environmental and genetic factors,[8] although no specific gene has been identified.[3,4] Suggested contributing factors include eye rubbing, atopy, ocular allergies, UV exposure, pollutants, and thyroid dysfunction.[3-5,9]

Keratoconus onset is typically during puberty,[4,8] but may not be identified until the second or third decade of life.[3] Progression is variable, generally continuing through to the third or fourth decades of life[8] when natural age-related stiffening of the cornea stabilises the condition.[4]

Current management involves refractive correction with glasses or contact lenses, rigid gas permeable contact lenses, intracorneal ring segments,[8] and photorefractive keratectomy.[1,2,4,9] Treatment of keratoconus requires keratoplasty or corneal collagen cross-linking (CXL).[2,4] CXL is a minimally invasive intervention that aims to halt keratoconus progression[8] by strengthening corneal tissue.[2,10] Treatment involves exposing the photosensitising agent riboflavin (Vitamin B2) to ultraviolet light (approximately 370 nm UVA),[2,4] triggering the formation of covalent bonds between collagen molecules,

fibrils and microfibrils, which increases corneal rigidity.[9,10] This strengthening of the cornea aims to prevent further thinning and therefore prevent the progression of keratoconus.[9,10]

Standard epithelium-off CXL (S-CXL) is the gold standard, with the Dresden protocol being most conventionally used,[8] though this procedure is contraindicated in patients with thinner corneas (<400 µm).[1,4] There are various methods of corneal epithelial debridement, it can be performed mechanically with scalpel blades, blunt knives and rotating brushes or chemically by applying dilute alcohol to the epithelium then mechanically removing the loosened surface layer.[11] An excimer laser or epithelial microkeratome can also be used to achieve epithelial removal.[11] De-epithelialisation facilitates riboflavin penetration of the stroma; however, it can cause complications including postoperative infections, pain,[12] visual blurring, corneal haze, corneal scarring[2] and impaired epithelial healing.[10,13]

Patients with corneas thinner than 400 µm can receive modified S-CXL treatments, however these are not standard practice and may not demonstrate results comparable to S-CXL.[14] One such option is Contact Lens-Assisted Cross-linking, whereby a UV barrier-free contact lens is infused with riboflavin and used to create a precorneal riboflavin layer.[15-17] This adds an extra 90-110 µm to the corneal thickness and decreases treatment depth which prevents any endothelial damage from the UV irradiation, however this technique could limit oxygen diffusion.[15-17] Another method includes using a hypo-osmolar riboflavin solution to induce corneal oedema and thereby increase corneal thickness,[9] yet a thickness of >400 µm may not always be reached.[15] Simply decreasing the strength of UVA irradiation or the duration of riboflavin exposure are also feasible options, yet this can reduce the impact of treatment.[14]

Epithelium-on (transepithelial) CXL was developed to avoid complications arising from epithelial removal, yet some studies have found it to be less effective than S-CXL[13] since the intact epithelium limits riboflavin permeation.[10,18] Methods of improving this technique have therefore been explored. A novel technique of transepithelial CXL uses iontophoresis[19] to improve riboflavin diffusion through corneal layers via a weak electrical current.[12,18] Iontophoresis-assisted transepithelial CXL (I-CXL) reduces pain and infection risk, produces quicker visual recovery, reduces treatment duration,[19] and is viable in thinner corneas, therefore it has the potential to become the future gold standard.[12,13,18]

Two systematic reviews from 2018 compared CXL with and without epithelial removal.[20,21] As transepithelial CXL is generally found to be less effective than S-CXL, one review suggested the transepithelial technique requires modification to become as successful as the S-CXL procedure.[21] The primary objective of this review is to determine if I-CXL efficacy is equal to that of S-CXL, and whether it could become a viable alternative, as it has the potential to avoid complications arising from de-epithelialisation while still preventing keratoconus progression. The secondary objective is to compare patient comfort and rate of adverse events associated with each procedure.

METHODS

Eligibility criteria

Types of studies

Case series, case reports, review articles and conference abstracts were excluded. All other peer-reviewed study designs were eligible for inclusion.

Types of participants

Studies involving participants of any age diagnosed with keratoconus were included. Studies involving participants who had undergone previous CXL or keratoplasty were excluded.

Types of interventions

Studies involving standard epithelium-off CXL and iontophoresis-assisted transepithelial CXL were included. Specifically, 30-minute irradiation with 3 mW/cm^2 UV-A light for S-CXL, and five minutes of iontophoresis for I-CXL were required for inclusion. Studies involving CXL in conjunction with other procedures or additional forms of CXL were excluded.

Types of outcome measures

The primary outcome measure was maximum keratometry (Kmax). Secondary outcome measures include corrected distance visual acuity (CDVA; LogMAR), uncorrected distance visual acuity (UCVA; LogMAR), central corneal thickness (CCT), spherical equivalent (SE), occurrence of adverse events and patient experience.

Included studies were required to contain the primary outcome measure and a minimum follow-up duration of six months.

Identification of studies

A search of the following electronic databases was performed on May 23rd, 2021; Medline (Ovid 1946 to May 21st 2021), Embase (Ovid 1947 to May 21st 2021), and CINAHL (EBSCO). Search terms are displayed in Table 1. Search results were limited to papers written in English. No restrictions were placed on years of publication or setting. Citation searching was performed from the reference lists of included studies. Hand searching of the Australian Orthoptic Journal, Volumes 12 to 52, was performed on May 23rd 2021, to locate publications not included in electronic databases.

Study selection

Search results from each database were exported to Endnote X9 (Clarivate Analytics).[22] A single reviewer removed duplicates and screened titles and abstracts of remaining studies. Studies deemed irrelevant were excluded and all remaining studies were

acquired in full via database links or through the La Trobe Library search to be assessed. Further studies not meeting inclusion criteria were excluded.

Data extraction

The following data was extracted from all included studies:

- Authors
- Year of publication
- Study design
- Study location
- Follow-up duration
- Characteristics of participants
  - Sample size
  - Age
  - Gender
  - Keratoconus inclusion criteria, defined progression or grade if identified
- Intervention and procedure performed
- Outcome measures and results

Table 1. Search terms#

Population	Intervention	Comparison
Keratocon*	CXL	CXL
KC	UV-CXL	UV-CXL
KCN	C3R	C3R
	C3-R	C3-R
	CCL	CCL
	Corneal collagen cross-link*	Corneal collagen cross-link*
	Corneal cross-link*	Corneal cross-link*
	Collagen cross-link*	Collagen cross-link*
	Cross-link*	Cross-link*
	Corneal collagen crosslink*	Corneal collagen crosslink*
	Corneal crosslink*	Corneal crosslink*
	Collagen crosslink*	Collagen crosslink*
	Crosslink*	Crosslink*
	Corneal collagen cross link*	Corneal collagen cross link*
	Corneal cross link*	Corneal cross link*
	Collagen cross link*	Collagen cross link*
	Cross link*	Cross link*
	AND	**AND**
	Transepitheli*	Standard
	Trans-epitheli*	Conventional
	Epitheli* on	Epitheli* off
	Epi* on	Epi* off
	Iontophore*	Epitheli* remov*
		Dresden

#Each column was combined with AND, each keyword was combined with OR

Critical appraisal

The methodology checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN)[23,24] were used to appraise the quality and risk of bias of included studies.

Data synthesis

Due to inconsistencies in outcome measures across included studies, data was not able to be pooled and analysed for a meta-analysis. Sub-group analysis was not possible, as individual participant data was not provided. A narrative synthesis was conducted, analysing and comparing available primary and secondary outcome measures from included studies at baseline and postoperative follow-up visits.

RESULTS

Search results

Searches across all three electronic databases resulted in a total of 378 studies. No additional studies were located from citation searching or hand searching. After duplicates were removed, 233 studies remained. All titles and abstracts were screened, and 12 studies were determined to be eligible for inclusion and were acquired in full. Of these, seven studies met eligibility criteria and were included. This process, along with reasons for exclusion, is represented in Figure 1.

Study characteristics

The characteristics of all seven included studies are outlined in Table 2, and the outcome measures at baseline and each follow-up period are detailed in Table 3. All studies were located in France or Italy, with publication years ranging from 2016 to 2019. Follow-up duration ranged from six to 36 months. Mean participant age ranged from 13 to 31 years, with one study exclusively including paediatric participants, and four studies including only adult participants. Three studies utilised the same sample of participants, each publishing data from various follow-up periods. All studies included the primary and at least one secondary outcome measure. Across all studies, duration and level of irradiation (UV-A light), and duration and current of iontophoresis for each CXL procedure was consistent.

Study quality

Lombardo et al (2016, 2017, 2019)[25,26,27] are all unmasked randomised controlled trials (RCTs) and were assessed via the SIGN RCT checklist.[23] The unmasked nature of these studies introduced an element of detection bias, therefore Lombardo et al (2016)[25] and Lombardo et al (2017)[26] were determined to be of high quality, but with relative risk of bias. Lombardo et al (2019)[27] was found to be of sound quality and greater risk of bias, as a single patient's data recorded at the last two follow-up visits was lost, altering mean values at 24 months follow-up. Additionally, nine percent of patients in both the control and study groups from Lombardo et al (2019)[27] were lost to follow-

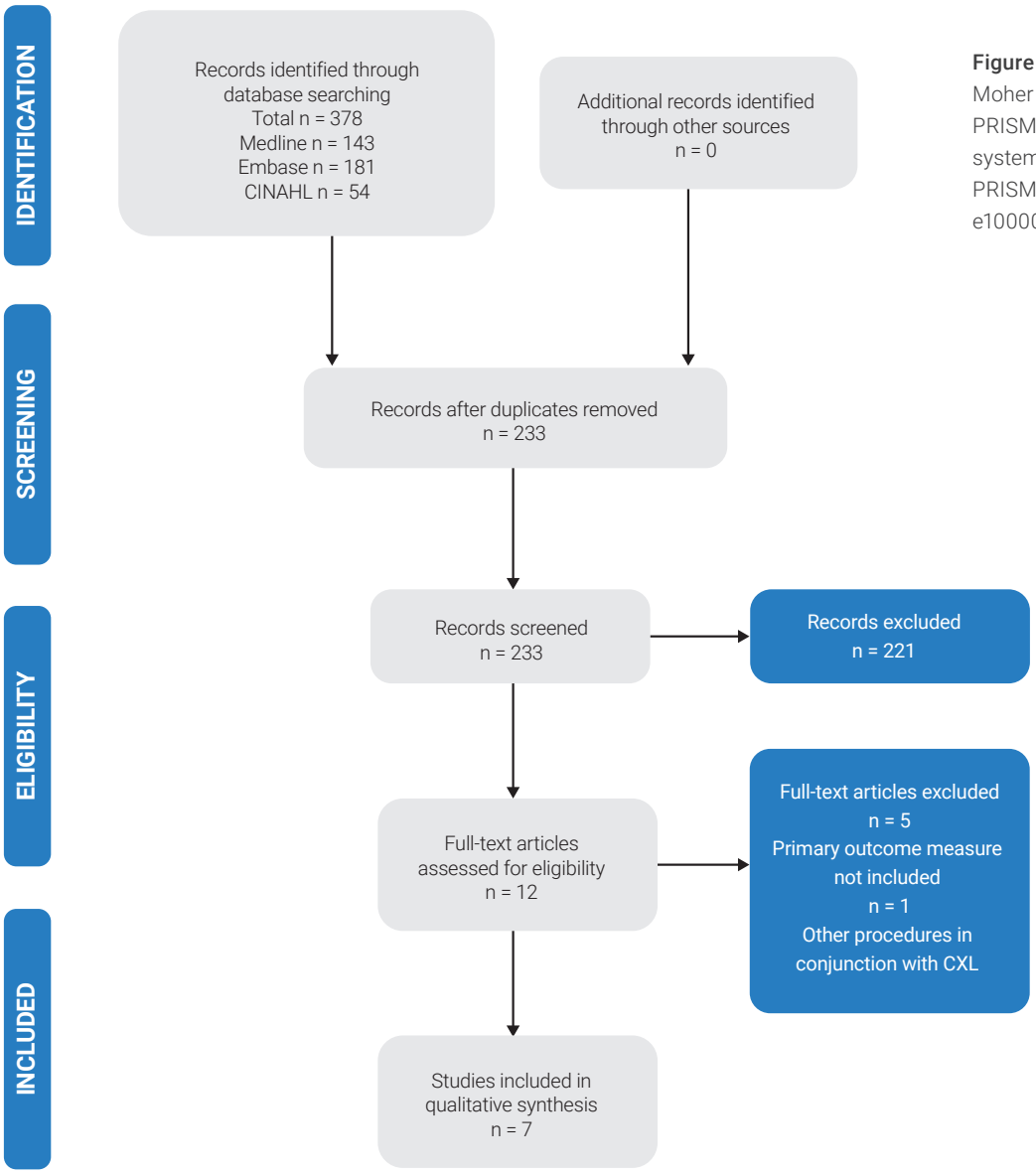

Figure 1. PRISMA flow diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7): e1000097.

up at 24 months, however, the authors concluded this did not introduce significant bias.

The four remaining studies followed a cohort study design and were appraised via the SIGN cohort study checklist.[24] Atia et al[28] and Vinciguerra et al[29] were found to be of fair quality and relative risk of bias as the follow-up duration was insufficient in both studies. Moreover, Vinciguerra et al[29] did not provide adequate information regarding three I-CXL patients lost to follow-up at 12 months and its potential impact. Buzzonetti et al[30] and Jouve et al[31] were determined to be of sound and high quality, respectively, with low risk of bias.

DISCUSSION

Findings

All studies found I-CXL to be a safe technique for halting keratoconus progression, resulting in less corneal haze and discomfort than S-CXL. Kmax and CDVA were measured in all studies and are therefore the most meaningful results. Following I-CXL Kmax either stabilised or increased, whereas following S-CXL significant flattening was commonly found. All studies, excluding Buzzonetti et al,[30] found CDVA improved substantially following I-CXL, and either stabilised or improved following S-CXL. CCT, SE and UDVA were measured in few studies, and SE data was lost in Lombardo et al (2019),[27] therefore these results were not reliable indicators of CXL efficacy. Four studies[25-27,29] concluded I-CXL results were comparable to that of S-CXL, however remaining studies[28,30,31] found I-CXL to be less effective, recommending S-CXL remain the gold standard.

Maximum keratometry

Atia et al[28] found Kmax was stable in both groups at one month, three months and six months postoperatively. Buzzonetti et al[30] found statistically insignificant Kmax flattening in the S-CXL group, and significant Kmax steepening in the I-CXL group at

36 months. Jouve et al[31] found Kmax to be stable following I-CXL, whereas statistically significant Kmax flattening was found following S-CXL. A significant negative correlation was found between Kmax values at baseline and 24 months postoperatively in both groups.

In Vinciguerra et al,[29] there was no significant difference in Kmax values at baseline (I-CXL=59.07 ±3.90; S-CXL=56.87 ±4.52) or progression rate between groups. At 12 months, a statistically significant reduction in Kmax was found only following S-CXL (I-CXL mean flattening=-0.31 ±1.87; S-CXL mean flattening=-1.05 ±1.51). The difference in Kmax flattening between the groups was statistically significant, indicating S-CXL was more effective.

In Lombardo et al (2016, 2017, 2019),[25,26,27] there were no significant differences in mean Kmax between groups at baseline (I-CXL=54.74 ±4.01; S-CXL=54.76 ±4.30) and Kmax progression 12 months prior to the study was similar. At six months, both groups demonstrated significant flattening of Kmax, yet at 12 months and 24 months, statistically significant Kmax flattening was found only following S-CXL. Mean Kmax at 24 months was 53.7 ±3.7D (p=0.07) in the I-CXL group, and 53.2 ±4.9D (p<0.001) in the S-CXL group, with a mean flattening of Kmax by -1.0 D in the I-CXL group and -1.5 D in the S-CXL group.

Keratoconus progression, as defined in Table 2 for each study, was found in ten I-CXL eyes and five S-CXL eyes in Buzzonetti et al,[30] eight I-CXL eyes and three S-CXL eyes in Jouve et al,[31] and two I-CXL eyes in Lombardo et al (2019).[27]

Corrected and uncorrected distance visual acuity

All studies measured CDVA and only three studies measured UCVA. Lombardo et al (2016)[25] measured best spectacle-corrected VA (BSCVA) which was taken as the CDVA measurement. In Lombardo et al (2016, 2017, 2019),[25,26,27] there was no significant difference in BSCVA between groups at baseline. At six months, BSCVA significantly improved in the I-CXL group only, and UCVA was not measured. When compared with baseline, at 12 months and 24 months UCVA significantly improved in both groups, whereas significant improvement in CDVA occurred only in the I-CXL group.

Atia et al[28] found CDVA improved significantly in the I-CXL group and stabilised in the S-CXL group by six months. Buzzonetti et al[30] found statistically significant improvement in CDVA in only the S-CXL group at 36 months. Jouve et al[31] found CDVA significantly improved following I-CXL across the 24 months, whereas significant improvement was only noted for one year following S-CXL. Vinciguerra et al[29] found a significant increase in CDVA in both groups at 12 months, with quicker improvement following I-CXL. Both groups showed a significant linear regression analysis.

Central corneal thickness

Five studies measured CCT. Atia et al[28] and Jouve et al[31] found CCT to be stable in both groups at six months and 24 months, respectively. Lombardo et al (2016)[25] found significant CCT thinning in the S-CXL group, with mild insignificant thinning in the I-CXL group at six months. Three days postoperatively, a significant CCT increase was found in the S-CXL group due to stromal oedema. Lombardo et al (2017, 2019)[26,27] found no significant CCT changes in either group at 12 months or 24 months.

Spherical equivalent

Four studies measured SE. Buzzonetti et al[30] did not find any significant changes in SE in either group over the 36 months. Lombardo et al (2016, 2017)[25,26] found SE to be significantly less myopic in only the I-CXL group at six months and 12 months. Lombardo et al (2019)[27] found a statistically significant reduction in myopia in both groups at 24 months, however the mean SE difference for the S-CXL group was caused by the loss of one participant's data at 12 and 24 months.

Occurrence of adverse events and patient experience

All studies performed slit lamp biomicroscopy to monitor for adverse events, yet only Lombardo et al (2016, 2017, 2019)[25,26,27] evaluated patient experience by using questionnaires to assess pain and symptoms after each procedure. Lombardo et al (2016),[25] Atia et al[28] and Jouve et al[31] placed bandage contact lenses (BCLs) on all S-CXL eyes, whereas Buzzonetti et al[30] and Vinciguerra et al[29] placed BCLs on eyes from both the I-CXL and S-CXL groups. Atia et al[28] and Jouve et al[31] reported no complications intraoperatively or postoperatively for either group. Vinciguerra et al[29] found all I-CXL participants presented with punctate keratitis day one postoperatively, resolving with the use of BCLs, except in one patient with central epithelial erosion which healed over two days. No other complications, including corneal haze, occurred in either group. Buzzonetti et al[30] found all S-CXL participants reported discomfort over the first week postoperatively, and corneal haze occurred in four eyes, eventually resolving. I-CXL participants tolerated treatment well, yet superficial punctate keratitis was found in nine eyes which resolved within a week.

Lombardo et al (2016)[25] found greater discomfort, epiphora and photophobia in the S-CXL group within three days postoperatively, yet after one week complaints or differences between groups were insignificant. Bulbar conjunctival hyperaemia and upper tarsal conjunctival papillae were greater following S-CXL. Corneal oedema was found in both groups within one week postoperatively, and at six months oedema remained in one S-CXL eye. Corneal haze grade 0.5 or higher was found in both groups at three months postoperatively, yet resolved in I-CXL participants and remained in six S-CXL eyes by six months. The corneal haze in these eyes was almost stable

at 12 months,[26] and was only found in two S-CXL eyes by 24 months.[27]

Strengths and limitations

This review is influenced by language bias as search results were limited to articles written in English. The search was conducted across three databases, with hand searching of only one journal publication, further reducing the number of studies located. Eligibility criteria excluded studies analysing additional methods of CXL alongside the two of interest, which helped refine and isolate treatment effects, but reduced available data comparing the two methods. Differences among included studies potentially impacted results. Restrictions on eligible CXL techniques attempted to control this and limit inter-surgeon variability, however procedure discrepancies still arose and completely eliminating inter-surgeon variability is not possible.

A low number of studies with small sample sizes were included in this review, reducing the significance and generalisability of the results. Many studies had incomplete data and inadequate follow-up durations, and heterogeneity of outcome measures and methods of acquiring measurements made data comparison less substantial. Individual study quality and bias, outlined in the study quality section, further limited the validity of review results. The three RCTs, a higher level of evidence,[32] were all found to contain bias. Cohort study designs are a lower level of evidence, and when retrospective in nature, this level is further reduced,[32] diminishing the reliability and generalisability of their results.

A further limitation is that all studies were performed in either Paris or Rome. This reduces the generalisability of their results and does not account for any potential impact from geographical influences.

A strength of this review is that across all studies, participant measurements from both groups were comparable at baseline, increasing reliability of results, however, findings from this review should certainly be applied with caution.

Contextualisation of findings

I-CXL Kmax changes were either comparable to or less significant than S-CXL, yet CDVA rapidly and significantly improved following I-CXL. Additionally, a lower occurrence and faster resolution of corneal haze and greater patient comfort demonstrates the advantages of I-CXL over S-CXL. While there were two studies that found I-CXL patients developed punctate keratitis when S-CXL patients did not, this resolved quickly with no further implications. Despite most studies finding I-CXL stabilised keratoconus and produced favourable visual outcomes, many recommended I-CXL only for use in those with thinner corneas or who are pain-sensitive.[25-31]

Buzzonetti et al[30] found a correlation between higher preoperative Kmax values and I-CXL efficacy, indicating I-CXL may be more effective for use in patients with advanced keratoconus, although Jouve et al[31] found no correlation. Buzzonetti et al[30] and Jouve et al[31] claimed that I-CXL could be advantageous in children, as procedure duration is reduced, and postoperative care is simpler. However, Lombardo et al (2017)[26] found average Kmax flattening increased after removing participants younger than 24 years from their analysis and identified younger age as a significant predictive factor for Kmax instability following I-CXL. Additionally, the two I-CXL patients who demonstrated keratoconus progression from Lombardo et al (2019)[27] were both under the age of 21 years. Conversely, Jouve et al[31] found age below 18 years was not a predictor for keratoconus progression. These contradictions and inconsistencies prove the need for further research, yet overall, studies suggested S-CXL remain the standard, especially in younger patients.[26,28,30,31]

There are various explanations for the reduced efficacy of I-CXL when compared with S-CXL. All included studies emphasised the remained interest in I-CXL and suggested adjustments that could be made to overcome these limitations and increase I-CXL effectiveness.[25-31]

Firstly, the corneal epithelium limits stromal penetration of riboflavin[20,21] resulting in a more superficial I-CXL effect.[28] This is demonstrated by the stromal depth of the demarcation line, the line representing the division between treated and untreated cornea.[28,33] Jouve et al,[31] Atia et al[28] and Vinciguerra et al[29] all found the demarcation line to be deeper and more visible in S-CXL participants. However, studies have found no correlation between demarcation line visibility and keratoconus progression following CXL,[26,31,34] and Vinciguerra et al[29] suggested differences in the I-CXL induced concentration gradient may be an alternate explanation for the poorer visibility.

Torres-Netto et al[35] believed poor stromal oxygenation to be reducing I-CXL efficacy, as they found the epithelium impedes oxygen supply to deeper layers, acting as a barrier and consuming higher rates of oxygen than the stroma. Jouve et al[31] also indicated the intact epithelium remains a barrier in I-CXL despite the use of iontophoresis. While aiming to overcome this barricade effect and increase riboflavin permeation, Lombardo et al (2016)[25] removed the precorneal mucin layer in their I-CXL procedure and found more effective outcomes for I-CXL than other included studies.

Buzzonetti et al[30] recommended enhanced fluence I-CXL as a potential improvement, as the 30% fluency increase and pulsed light irradiation improves stromal oxygen diffusion and depth of treatment. Jouve et al[31] recommended increasing iontophoresis duration, supported by Torres-Netto et al,[35] who also suggested

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Table 2. Study characteristics

Study	Study Type	Location and follow-up period	Participant demographics (S-CXL/I-CXL)	Keratoconus inclusion criteria, defined progression and grade (if applicable)
Atia et al, 2018[28]	Prospective, observational, non-randomised clinical study	Paris, France 6 months	**N eyes** 30/30 **Mean age** 25 ± 6.44/ 29 ± 7.36 **N female** 7/8	**Inclusion criteria:** Progressive keratoconus, Kmax ≤60D, CCT ≥400µm. **Progression:** Corneal thickness decrease of ≥30µm and Kmax increase of 1.00D over 6-months. **Mean keratoconus grade:** 2.2 ± 0.80 Amsler stage.
Buzzonetti et al, 2019[30]	Retrospective study	Rome, Italy 36 months	**N eyes** 20/20 **Mean age** 13 ± 3.5/ 14 ± 4 **N female** NA/NA 7 total	**Inclusion criteria:** Documented keratoconus diagnosis. **Progression:** Kmax increase of 1.00 D over 36-months. **Mean keratoconus grade:** No grade.
Jouve et al, 2017[31]	Prospective, observational, non-randomised clinical study	Paris, France 24 months	**N eyes** 40/40 **Mean age** 24.8 ± 8/ 27.7 ± 7.2 **N female** 12/16	**Inclusion criteria:** Progressive keratoconus, Kmax ≤60D, pachymetry ≥400µm at thinnest point, CDVA ≥20/80. **Progression:** Kmax increase of ≥0.75D or CCT decrease of ≥30 µm over last 6 months, or refractive astigmatism worsening of ≥0.75D over last 12 months. **Mean keratoconus grade:** 3.3 ± 0.5 Amsler stage, and 1.2 ± 0.4 OCT classification by Sandali et al.[39]
Lombardo et al, 2016[25]	Ongoing prospective, unmasked, randomised controlled trial	Rome, Italy 6 months	**N eyes** 12/22 **Mean age** 29.4 ± 5.6/ 31 ± 6.6 **N female** 4/3	**Inclusion criteria:** Confirmed diagnosis of progressive keratoconus. **Progression:** Increase of ≥1D in Kmax over the last 12 months, as documented by computerised Placido disk corneal topography. **Mean keratoconus grade:** No grade.
Lombardo et al, 2017[26]	Prospective, unmasked, randomised controlled trial	Rome, Italy 12 months	Refer to Lombardo et al, 2016[25]	Refer to Lombardo et al, 2016[25]
Lombardo et al, 2019[27]	Unmasked, randomised controlled trial	Rome, Italy 24 months	Refer to Lombardo et al, 2016[25]	Refer to Lombardo et al, 2016[25]
Vinciguerra et al, 2016[29]	Comparative, prospective, non-randomised, single-centre interventional study	Milan, Italy 12 months	**N eyes** 20/20 **Mean age** 28.2 ± 8.5/ 27.8 ± 6.4 **N female** NA/NA	**Inclusion criteria:** Documentation of keratoconus progression. **Progression:** Progression not defined. **Mean keratoconus grade:** No grade.

EDTA ethylenediaminetetraacetic acid, **Kmax** maximum keratometry, **CDVA** corrected distance visual acuity, **UCVA** uncorrected visual acuity, **CCT** central corneal thickness, **ECD** endothelial cell density, **BSCVA** best spectacle-corrected visual acuity, **CSF** contrast sensitivity function, **SE** spherical equivalent, **IOP** intraocular pressure

	CXL procedure	Main outcome measures
	S-CXL epithelial debridement (method not stated), 0.1% riboflavin solution in 20% dextran every 2 mins for 30 mins, 30-min irradiation with 3-mW/cm^2 UV-A light at 5cm (5.4 J/cm^2 surface dose) while riboflavin drops were instilled every 5 mins, BCL applied. **I-CXL** passive electrode on forehead, active electrode on cornea and filled with riboflavin solution, current intensity gradually increased from 0.2mA to 1.0mA over 5 mins, 9-min irradiation with 10mW/cm^2 UV-A light at 5cm (5.4 J/cm^2 surface dose).	CDVA (LogMAR) Kmax (D) CCT (µm) – AS-OCT Central epithelial thickness (µm) Minimum corneal pachymetry (µm)
	S-CXL manual epithelial debridement with a blunt knife, 0.1% riboflavin solution in 20% dextran applied for 10 mins, 30-minute irradiation with 3-mW/cm^2 UV-A light while riboflavin solution was instilled every 3 mins, BCL applied. **I-CXL** Passive electrode on forehead, active electrode on cornea and filled with riboflavin solution (0.1% riboflavin, EDTA, trometamol), current intensity gradually increased from 0.5mA to 1.0mA over 5 mins, 9-min irradiation with 10mW/cm2 UV-A light, BCL applied.	CDVA (LogMAR) Manifest SE (D) Kmax (D) Posterior corneal steepening (µm) Thickness of the thinnest point (µm)
	S-CXL manual debridement of central 7.0-9.0mm epithelium with a blunt spatula, 0.1% riboflavin solution in 20% dextran applied every 2 mins for 20 mins, 30-min irradiation with 3-mW/cm^2 UV-A light at 5cm (5.4 J/cm^2 total energy) while riboflavin drops were instilled every 5 mins, BCL applied. **I-CXL** passive electrode on forehead, active electrode on cornea and filled with riboflavin solution, current intensity set to 1.0mA for 5 mins, 9-min irradiation with 10mW/cm^2 UV-A light at 5cm (5.4-J/cm^2 total energy).	Kmax (D) CCT (µm) Minimal corneal thickness (µm) CDVA (LogMAR) ECD (cells/mm^2)
	S-CXL central 10mm epithelium removed with an Amoils brush (epithelial scrubber), 0.1% riboflavin solution in 20% dextran applied every 3 mins for 30 mins, 30-min irradiation with 3-mW/cm^2 UV-A light (5.4 J/cm^2 total energy) while 0.025% riboflavin drops were instilled every 3 mins, 2 drops of ofloxacin 0.3% instilled, BCL applied. **I-CXL** central cornea applanated with a Biopore membrane for 3 secs removing pre-corneal mucin layer, passive electrode on forefront of eye, active electrode on cornea and filled with riboflavin solution (0.1% riboflavin, EDTA, trometamol), current intensity of 1.0mA for 5 mins, 9-min irradiation with 10mW/cm^2 UV-A light at 56mm (5.4-J/cm^2 total energy), chilled 0.9% chloride sodium solution instilled every 3 mins during irradiation.	BSCVA (LogMAR) CSF (Pelli-Robson) SE (D) Kmax (D) CCT (µm) ECD (cells/mm^2)
	Refer to Lombardo et al, 2016[25]	UDVA (LogMAR) CDVA (LogMAR CSF (Pelli-Robson) SE (D) Kmax (D) CCT (µm) ECD (cells/mm2) IOP (mmHg)
	Refer to Lombardo et al, 2016[25]	Refer to Lombardo et al, 2017[26]
	S-CXL central 9mm epithelium removed with an Amoils brush (epithelial scrubber), 0.1% riboflavin solution in 20% dextran applied every minute for 30 mins, 30-min irradiation with 3-mW/cm^2 UV-A light (5.4 J/cm^2 total energy), BCL applied. **I-CXL** active electrode placed on cornea and filled with riboflavin solution (0.1% riboflavin, EDTA, trometamol), current intensity of 1.0mA for 5 mins, 9-min irradiation with 10mW/cm^2 UV-A light at 45mm (5.4-J/cm^2 total energy), BCL applied.	CDVA (LogMAR) Sphere (D) Cylinder (D) Kmax (D) ECD (cells/mm^2) Minimum pachymetry (µm)

Table 3. The primary and secondary outcome measures at baseline, 1 , 3, 6, 12, 24 and 36-months post CXL procedure

Study	Baseline	1 month	3 months
Atia et al, 2018[28]	**Kmax** (Orbscan IIz) S-CXL = 49.90 ± 6.30 I-CXL = 50.80 ± 5.20 **CDVA** (Snellen) S-CXL = 0.19 ± 0.23 I-CXL = 0.27 ± 0.22 **CCT** (AS-OCT) S-CXL = 467 ± 35.9 I-CXL = 464 ± 34		
Buzzonetti et al, 2019[30]	**Kmax** (Sirius Scheimpflug Camera) S-CXL = 47.2 ± 3.5 I-CXL = 47.2 ± 3.5 **CDVA** S-CXL = 0.2 ± 0.1 I-CXL = 0.2 ± 0.1 **SE** S-CXL = -1.7 ± 0.8 I-CXL = -2.2 ± 2.3		
Jouve et al, 2017[31]	**Kmax** S-CXL = 49.9 ± 4.5 I-CXL = 50.9 ± 5.6 **CDVA** S-CXL = 0.19 ± 0.17 I-CXL = 0.24 ± 0.23 **CCT** (AS-OCT) S-CXL = 473 ± 37 I-CXL = 469 ± 32	**Kmax** S-CXL = 50.2 ± 4.5 (p = 0.23) I-CXL = 50.3 ± 6.2 (p = 0.53) **CDVA** S-CXL = 0.2 ± 0.17 (p = 0.09) I-CXL = 0.22 ± 0.24 (p = 0.08) **CCT** S-CXL = 471 ± 37 (p = 0.11) I-CXL = 467 ± 34 (p = 0.18)	**Kmax** S-CXL = 49.5 ± 5.4 (p = 0.12) I-CXL = 49.8 ± 5 (p = 0.48) **CDVA** S-CXL = 0.14 ± 0.16 (p = 0.39) I-CXL = 0.1 ± 0.1 (p = 0.01) **CCT** S-CXL = 468 ± 34 (p = 0.14) I-CXL = 476 ± 35 (p = 0.37)

6 months	12 months	24 months	36 months
Kmax S-CXL = 50.10 ± 6.40 (*p* = 0.17) I-CXL = 50.90 ± 5.00 (*p* = 0.79) **CDVA** S-CXL = 0.18 ± 0.20 (*p* = 0.34) I-CXL = 0.20 ± 0.2 (*p* = 0.003) **CCT** S-CXL = 466 ± 41.9 (*p* = 0.75) I-CXL = 460 ± 34 (*p* = 0.48)			
	Kmax S-CXL = 48.0 ± 3.2 (*p* = 0.7) I-CXL = 48.0 ± 3.2 (*p* = 0.7) **CDVA** S-CXL = 0.2 ± 0.1 (*p*= 0.4) I-CXL = 0.2 ± 0.1 (*p* = 0.4) **SE** S-CXL = -2.5 ± 2.2 (*p* = 0.6) I-CXL = -1.8 ± 2.4 (*p* = 0.6)	**Kmax** S-CXL = 48.1 ± 2.5 (*p* = 0.7) I-CXL = 49.4 ± 4.3 (*p* = 0.1) **CDVA** S-CXL = 0.2 ± 0.1 (*p* = 0.4) I-CXL = 0.2 ± 0.1 (*p* = 0.4) **SE** S-CXL = -2.0 ± 2.4 (*p* = 0.6) I-CXL = -1.8 ± 2.4 (*p* = 0.6)	**Kmax** S-CXL = 48.0 ± 2.5 (p = 0.6) I-CXL = 50.1 ± 4.7 (p = 0.004) **CDVA** S-CXL = 0.1 ± 0.1 (p = 0.03) I-CXL = 0.2 ± 0.1 (p = 0.6) **SE** S-CXL = -1.3 ± 1.3 (p = 0.4) I-CXL = -2.2 ± 2.4 (p = 0.9)
Kmax S-CXL = 49.4 ± 5.1 (*p* = 0.08) I-CXL = 50.3 ± 5.4 (*p* = 0.51) **CDVA** S-CXL = 0.18 ± 0.23 (*p* = 0.23) I-CXL = 0.12 ± 0.2 (*p* = 0.003) **CCT** S-CXL = 468 ± 36 (*p* = 0.32) I-CXL = 469 ± 33 (*p* = 0.25)	**Kmax** S-CXL = 49.2 ± 4.2 (*p* = 0.02) I-CXL = 51 ± 6.2 (*p* = 0.63) **CDVA** S-CXL = 0.11 ± 0.12 (*p* = 0.04) I-CXL = 0.2 ± 0.28 (*p* = 0.03) **CCT** S-CXL = 467 ± 33 (*p* = 0.1) I-CXL = 466 ± 35 (*p* = 0.17)	**Kmax** S-CXL = 48.8 ± 4.2 (*p* < 0.01) I-CXL = 51.1 ± 5.2 (*p* = 0.56) **CDVA** S-CXL = 0.10 ± 0.11 (*p* = 0.04) I-CXL = 0.17 ± 0.2 (*p* = 0.01) **CCT** S-CXL = 468 ± 34 (*p* = 0.1) I-CXL = 462 ± 39 (*p* = 0.16)	

Table 3 continued next page

Table 3. The primary and secondary outcome measures at baseline, 1 , 3, 6, 12, 24 and 36-months post CXL procedure

Study	Baseline	1 month	3 months
Lombardo et al, 2016[25] Baseline – 6 months **Lombardo et al, 2017[26] Baseline – 12 months** **Lombardo et al, 2019[27] Baseline – 24 months**	**Kmax** (Placido disk corneal topography & AS-OCT) S-CXL = 54.76 ± 4.30 I-CXL = 54.74 ± 4.01 **BSCVA/CDVA** (ETDRS chart) S-CXL = 0.06 ± 0.10 I-CXL = 0.12 ± 0.20 **UCVA** (ETDRS chart) S-CXL = 0.65 ± 0.30 I-CXL = 0.80 ± 0.19 **CCT** (Placido disk corneal topography & AS-OCT) S-CXL = 494 ± 34 I-CXL = 484 ± 37 **SE** (Placido disk corneal topography) S-CXL = -1.75 ± 2.12 I-CXL = -2.64 ± 2.41		
Vinciguerra et al, 2016[29]	**Kmax** (CSO EyeTop Topographer)[40] S-CXL = 56.87 ± 4.52 I-CXL = 59.07 ± 3.90 **CDVA** (ETDRS chart)[40] S-CXL = 0.16 ± 0.08 I-CXL = 0.25 ± 0.15	**Kmax** S-CXL = 57.36 ± 4.63 (p = 0.30) I-CXL = 59.63 ± 3.44 (p = 0.05) **CDVA** S-CXL = 0.15 ± 0.08 (p = 0.70) I-CXL = 0.25 ± 0.22 (p = 0.13)	**Kmax** S-CXL = 56.5 ± 4.35 (p = 0.40) I-CXL = 59.45 ± 3.71 (p = 0.96) **CDVA** S-CXL = 0.12 ± 0.08 (p = 0.10) I-CXL = 0.20 ± 0.18 (p = 0.18)

All values are presented as mean ± standard deviation.
Kmax maximum keratometry, **CDVA** corrected distance visual acuity, **BSCVA** best spectacle-corrected visual acuity, **ETDRS** Early Treatment Diabetic Retinopathy Study, **UCVA** uncorrected visual acuity, **CCT** central corneal thickness, **SE** spherical equivalent
***Lombardo et al (2016, 2017)[25,26] did not provide the average measurements for Kmax or SE at 6 months or 12 months, the average flattening or change from the baseline measurements were provided

	6 months	12 months	24 months	36 months
	Kmax*	**Kmax***	**Kmax**	
	S-CXL = (-)0.86 ± 0.89	S-CXL = -0.82 ± 1.20	S-CXL = 53.2 ± 4.9	
	(*p* = 0.006)	(*p* = 0.04)	(*p* < 0.001)	
	I-CXL = (-)0.72 ± 1.20	I-CXL = -0.52 ± 1.30	I-CXL = 53.7 ± 3.7	
	(*p* = 0.01)	(*p* = 0.06)	(*p* = 0.07)	
	BSCVA/CDVA	**CDVA**	**CDVA**	
	S-CXL = 0.01 ± 0.07	S-CXL = 0.03 ± 0.09	S-CXL = 0.03 ± 0.09	
	(*p* = 0.08)	(*P* = 0.10)	(*p* = 0.38)	
	I-CXL = 0.01 ± 0.10	I-CXL = 0.03 ± 0.10	I-CXL = 0.04 ± 0.13	
	(*p* = 0.001)	(*p* = 0.003)	(*p* = 0.04)	
	UCVA	**UCVA**	**UCVA**	
	NA	S-CXL = 0.32 ± 0.25	S-CXL = 0.32 ± 0.29	
		(*p* < 0.001)	(*p* = 0.01)	
		I-CXL = 0.52 ± 0.28	I-CXL = 0.48 ± 0.36	
		(*p* < 0.001)	(*p* < 0.001)	
	CCT	**CCT**	**CCT**	
	S-CXL = 481 ± 29	S-CXL = 493 ± 33	S-CXL = 499 ± 21	
	(*p* = 0.03)	(*p* = 0.80)	(*p* = 0.52)	
	I-CXL = 480 ± 33	I-CXL = 493 ± 35	I-CXL = 491 ± 27	
	(*p* = 0.50)	(*p* = 0.07)	(*p* = 0.35)	
	SE *	**SE ***	**SE**	
	S-CXL = +0.24 ± 0.77	S-CXL = +0.21 ± 0.76	S-CXL = -0.94 ± 1.23	
	(*p* = 0.32)	(*p* = 0.38)	(*p* = 0.05)	
	I-CXL = +0.65 ± 1.20	I-CXL = +0.71 ± 1.44	I-CXL = -1.83 ± 1.55	
	(*p* = 0.02)	(*p* = 0.03)	(*p* = 0.03)	
	Kmax	**Kmax**		
	S-CXL = 56.11 ± 4.61	S-CXL = 55.82 ± 4.29		
	(*p* = 0.05)	(*p* = 0.005)		
	I-CXL = 58.69 ± 3.45	I-CXL = 58.22 ± 3.90		
	(*p* = 0.35)	(*p* = 0.44)		
	CDVA	**CDVA**		
	S-CXL = 0.10 ± 0.08	S-CXL = 0.10 ± 0.08		
	(*p* = 0.04)	(*p* = 0.03)		
	I-CXL = 0.12 ± 0.13	I-CXL = 0.12 ± 0.15		
	(*p* = 0.0004)	(*p* = 0.0003)		

increasing irradiation duration, and lowering irradiance levels, however this presents issues with treatment duration.

The energy dose used in CXL procedures, typically 5.4 J/cm^2, may be further hindering I-CXL impact as the corneal epithelium limits UV-A transmittance by 20%, therefore the total energy in I-CXL is less than in S-CXL.[21,31,36] Four studies[26,28,29,31] suggested increasing the total UV-A energy dose in I-CXL to 6.5 J/cm^2, as this will overcome the epithelial filtering effect.[36]

Currently, there is no sole outcome measure that can reliably monitor keratoconus progression following CXL. Most studies use Kmax as the main outcome measure to determine success of CXL, however it should not be considered in isolation as it does not reflect changes in visual acuity or refraction.[37] Demarcation line depth is another frequently used outcome measure, yet according to Lombardo et al (2017)[26] this biomarker has not been validated due to the fact that there is no clear correlation between demarcation line visibility and keratoconus progression, as mentioned previously.

Atia et al[28] suggested epithelial mapping may be more sensitive in identifying stromal surface changes caused by CXL than corneal topography and may give an earlier indication of CXL efficacy. Keratoconic corneas demonstrate epithelial thinning over the apical cone and a surrounding annulus of epithelial thickening, creating a doughnut-like pattern, which attempts to regulate the corneal surface.[38] Following CXL, epithelial remodelling occurs, which involves peripheral thinning surrounding the cone causing a reduction in the doughnut shape and an increase in homogeneity of the epithelial thickness distribution.[38]

Multiple biomarkers should be evaluated to determine CXL success. Further studies with a greater variety of outcome measures, including manifest refraction, CCT, corneal topography including Kmax, and the distribution of corneal epithelial thickness,[26] will be able to give a clearer indication of CXL efficacy in halting keratoconus progression.

CONCLUSION

Ultimately, no clear conclusions can be drawn regarding whether I-CXL could become a viable alternative for S-CXL. However, it can be confirmed that I-CXL is a safe and largely effective procedure for keratoconus stabilisation. More randomised control trials with larger sample sizes and longer follow-up periods are required, particularly in varied geographical locations. Additionally, research exploring these suggested modifications to I-CXL and the use of I-CXL in specific populations, such as different age groups and severity of keratoconus, is necessary.

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